REMARKS

Claim 1 has been amended. Claims 1 and 8-10 are pending in the present application. Applicants submit that the amended claim is supported throughout the specification, including at least at page 4, lines 32-35. Reconsideration of the rejections of the claims is respectfully requested.

The specification has been amended to correct a typographical error.

Accompanying Applicants' response is the Declaration of Nicholas van Bruggen under 37 CFR 1.132 (hereinafter referred to as the "Declaration"), a co-inventor of the present application, describing the state of the art at the time of the filing of the present application.

Petition for Extension of Time

A three-month extension of time is requested extending the date for timely response to December 25, 2002.

Rejection of Claims Under § 112, First Paragraph

The Examiner rejected claims 1 and 8-10 under 35 U.S.C. § 112, first paragraph, as allegedly lacking an enabling disclosure. The Examiner contends that there is no guidance or objective evidence that the claimed method would be effective for reducing non-VEGF mediated cerebral edema. Applicants have amended claim 1 to recite "cerebral edema mediated by VEGF". Applicants, therefore, respectfully request withdrawal of the rejection.

Rejection of Claims Under § 103(a)

1) The Examiner rejected claims 1 and 8-10 under 35 U.S.C. § 103(a) as being obvious in view of WO 94/10202, Ferrara et al., published May 11, 1994. Applicants respectfully traverse this rejection.

To establish *prima facie* obviousness, three basic criteria must be met, namely: 1) suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; 2) a reasonable expectation of success; and 3) the references when combined must teach or suggest all the claim limitations. MPEP §2142. Applicants argue that all of these

requirements have not been met, in the least, because WO 94/10202 does not provide a reasonable expectation of success of achieving the claimed invention.

The Examiner asserts that WO 94/10202 discloses treating edema associated with brain tumors with VEGF antagonists. However, as discussed in the Declaration by Dr. Van Bruggen, at the time of the filing of the present application, it could not be predicted if VEGF was a causative agent of edema or if an antagonist of VEGF could successfully treat cerebral edema. Dr. Van Bruggen explains that this lack of predictability is because of contradictory experimental observations cited in the literature and lack of direct evidence of causation. *See* Declaration at paragraphs 3-13.

As explained by Dr. Van Bruggen, at the time of filing the application, the literature presented contradictory evidence concerning VEGF involvement in edema. See Declaration at paragraphs 4 to 8. In some studies, VEGF expression was more strongly correlated with tumor vascularity rather than cerebral edema. See Berkman et al, 1993, *J. Clin. Investigation,* 91: 153-159 at page 157. Hayashi et al. (1998, *J. Cereb. Blood Flow Metab.,* 18:887-895) reported that VEGF itself, when applied topically to the surface of a reperfused rat brain after transient cerebral artery occlusion, reduced ischemic brain damage, infarct volume, and edema formation. A more recent study of glioblastomas failed to show a significant correlation between the degree of VPF and the degree of peritumoral edema. See Vaquero et al., 2000, *J. Neuro-Oncology 49:49-55* at page 49. The authors state that their results suggest that factors other than intratumoral presence of VPF may contribute to the development of peritumoral edema. Vaquero et al., *supra.*

In other studies, such as those of Kalkanis et al., 1996, *J. Neurosurg.* 85:1095-1101 and Strugar et al., 1994, *J. Neurosurg.* 81:560-566, a strong correlation was found between expression of VEGF and edema but no evidence of direct causation of edema by VEGF was presented. See Declaration at paragraphs 6, 7 and 16. Although it was hypothesized that VEGF played a role in edema formation, this hypothesis could not be verified without an antagonist effective in an animal model.

At the time of the filing of the above referenced application, one skilled in the art could not predict if VEGF was a causative agent of cerebral edema because of the lack of VEGF antagonists effective in a rodent model for the treatment of cerebral edema. *See* Declaration at paragraphs 7-9. Because the majority of research studies are performed on rodents, the lack of a

suitable pharmacological VEGF antagonist effective in either rat or mouse prevented a clear understanding of the contribution of VEGF in the pathogenesis of stroke and related disorders. *See* van Bruggen et al., 1999, *J. Clin. Investigation* 104:1613-1629 at page 1613. Those skilled in the art recognized that VEGF's suggested role in cerebral edema formation could not be proved definitively without an effective VEGF antagonist. *See* Kalkanis et al., 1996, *J. Neurosurg.*, 85:1095-1101 at page 1099, second column, second full paragraph.

As stated by Dr. Van Bruggen, it also could not be predicted, at the time of the invention, if the inhibition of VEGF by an antagonist would be sufficient to inhibit cerebral edema formation *in vivo* because of a lack of an effective antagonist that could be tested in a suitable animal model. Declaration at paragraphs 7-10. The antibody, A4.6.1, described in WO 94/10202 could not have been used to study edema in a rodent model because it is specific for human VEGF and did not neutralize the activity of rat VEGF. This aspect of A4.6.1 prevented its use in animal model studies in which endogenously expressed VEGF is important to pathology.

Therefore, it would not have been obvious to use the VEGF antagonist disclosed by WO 94/10202 to treat cerebral edema. There was no reasonable expectation of success that cerebral edema could be successfully treated *in vivo* with a VEGF antagonist because of contradictory evidence in the literature and lack of direct evidence of causation.

Applicants respectfully request withdrawal of the rejection on this basis.

2) The Examiner rejected claims 1 and 8-10 under 35 U.S.C. § 103(a) as being obvious over Criscuolo, R., 1994, *Yale J. Bio. Med.*, 66:277-314 or Fischer et al., 1998, *Mol. Brain Res.*, 60:98-97 in view of WO 94/10202. Applicants respectfully traverse this rejection, in the least, because these references do not disclose all of the elements of the claimed invention.

The Examiner asserts that Criscuolo teaches a method of reducing cerebral edema in a mammal comprising administering an hVEGF antagonist (dexamethasone) to reduce the volume of cerebral brain edema in the brain of the mammal. Applicants respectfully disagree. Dexamethasone is not known to be an antagonist of VEGF.

Antagonists of VEGF act by interfering with the binding of VEGF to a cellular receptor, by incapacitating or killing cells that have been activated by VEGF, or by interfering with vascular endothelial cell activation after VEGF binding to a cellular receptor. *See* Specification, page 7 at lines 11-15. As discussed by Dr. Van Bruggen, scientific literature reports that

coinjection of dexamethasone with VEGF or pretreatment with dexamethasone less than an hour prior to VEGF injection failed to alter the extent of vascular extravastion induced by VEGF alone in glioma and endothelial cells. *See* Criscuolo, at page 304. If dexamethasone were an antagonist of VEGF, one would have expected coinjection of dexamethasone with VEGF to decrease the extent of vascular extravasation. *See also,* the Declaration of Dr. van Bruggen, submitted with this Amendment.

In addition, as discussed by Dr. Van Bruggen in the Declaration, contradictory reports exist in the literature about the role of VEGF in cerebral edema. In a later paper co-authored by Criscuolo, the relationship between VEGF (identified therein as VPF) and peritumoral edema was studied in metastatic brain tumor tissue samples. See Strugar et al., 1994, *J. Neurosurg.,* 81:560. The author reports that the study indicates that regardless of origin of the metastases, there is a high correlation between presence of VPF, vasogenic edema, and neovascularization. However, the authors go on to state that although highly correlative, these observations do not prove that VPF is either the responsible agent for peritumoral brain edema and angiogenesis or that VPF represents a marker for metastatic potential. *See* Strugar et al. *supra* at page 565.

The Examiner also asserts that Fischer et al. teaches a method of reducing cerebral edema in a mammal comprising administering an hVEGF antagonist (methohexital or thiopental) to reduce the volume of cerebral brain edema in the brain of the mammal. Applicants respectfully disagree. The barbiturates methohexital and thiopental are not known to be antagonists of VEGF.

As discussed previously, antagonists of VEGF act by interfering with the binding of VEGF to a cellular receptor, by incapacitating or killing cells that have been activated by VEGF, or by interfering with vascular endothelial cell activation after VEGF binding to a cellular receptor. *See* Specification, page 7 at lines 11-15. As discussed by Dr. Van Bruggen, the scientific literature reports that compared to brain derived microvascular endothelial cells (BMEC) treated with VEGF only, treatment of BMEC with VEGF and methohexital or thiopental did not reduce the VEGF-induced permeability of the BMEC monolayer. *See* Fischer et al. at page 94, Figure 4. If methohexital or thiopental were antagonists of VEGF, one would have expected a reduction in the permeability of the BMEC monolayer. *Id. See also,* the Declaration of Dr. van Bruggen.

The instant claims recite a method of treating cerebral edema mediated by VEGF comprising administering an effective amount of hVEGF antagonist. Criscuolo does not teach or suggest that dexamethasone is an antagonist of VEGF. Fischer et al. does not teach or suggest that methohexital or thiopental are antagonists of VEGF.

WO 94/10202 does not remedy the shortcomings of Criscuolo and Fischer et al. As discussed previously, at the time of the filing of the present invention, one skilled in the art could not predict (1) if VEGF was a causative agent of cerebral edema because of contradictory experimental observations cited in the literature, (2) if VEGF was a causative agent of cerebral edema because of the lack of an animal model for the treatment of cerebral edema with VEGF antagonists, and (3) if anti-VEGF antibodies or other VEGF antagonists would be effective to treat cerebral edema *in vivo* because of the lack of an animal model . *See* Declaration of Dr. van Bruggen at paragraphs 3-9.

Accordingly, the cited references, alone or in combination, do not teach or suggest a method of treating cerebral edema with VEGF antagonists. Applicants respectfully request withdrawal of these rejections.

CONCLUSION

Claims 1 and 8-10 are in condition for allowance. Notice to that effect is earnestly solicited. The Examiner is invited to telephone the undersigned for clarification of any of the amendments or remarks or to otherwise facilitate prosecution of the application.

Respectfully submitted,

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